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Evolving resistance landscape in gram-negative pathogens: An update on β-lactam and β-lactam-inhibitor treatment combinations for carbapenem-resistant organisms

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Abstract

Antibiotic resistance has become a global threat as it is continuously growing due to the evolution of β-lactamases diminishing the activity of classic β-lactam (BL) antibiotics. Recent antibiotic discovery and development efforts have led to the availability of β-lactamase inhibitors (BLIs) with activity against extended-spectrum β-lactamases as well as *Klebsiella pneumoniae* carbapenemase (KPC)-producing carbapenem-resistant organisms (CRO). Nevertheless, there is still a lack of drugs that target metallo-β-lactamases (MBL), which hydrolyze carbapenems efficiently, and oxacillinases (OXA) often present in carbapenem-resistant *Acinetobacter baumannii*. This review aims to provide a snapshot of microbiology, pharmacology, and clinical data for currently available BL/BLI treatment options as well as agents in late stage development for CRO harboring various β-lactamases including MBL and OXA-enzymes.

KEYWORDS
Acinetobacter baumannii, Enterobacterales, *Pseudomonas aeruginosa*, β-lactamase, β-lactamase inhibitor

1 | INTRODUCTION

Antimicrobial resistance (AMR) to a variety of β-lactam antibiotics is rising globally. In particular, increasing resistance is observed in gram-negative bacteria including Enterobacterales, *Pseudomonas aeruginosa*, and *Acinetobacter* species resulting in a threat to global public health. These organisms are often classified based on their phenotypic profile and as such can be termed Carbapenem Resistant Organisms (CRO), and are further defined by whether or not they produce carbapenemase enzymes.[1] For example, recent epidemiological studies showed a doubling of carbapenem-resistant Enterobacterales (CRE) during the last 2 decades and an ongoing trend of increasing carbapenem-resistance worldwide.[2,3] The current burden of AMR has emerged to become one of the leading public health threats and attributed to ~1.2 million deaths in 2019.[4] Without the development of new antimicrobials, it is estimated that 10 million people will die from AMR bacteria by 2050.[5] International societies such as the Infectious Diseases Society of America (IDSA) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) have made it their mission to provide guidance on the treatment of infections due to antimicrobial-resistant bacteria.[6–8]

Gram-negative resistance to β-lactam antibiotics is most commonly due to the presence of β-lactamases, which are able to hydrolyze the β-lactam amide bond resulting in an open ring that is not able to bind to the penicillin binding protein (PBP) site.[2,3,9] β-lactamases are classified by their protein sequence and the resulting amino acid motifs in four Ambler classes: A, B, C, and D (Table 1). Classes A, C, and D have an active serine catalytic site (i.e., serine-β-lactamases), whereas class B requires a zinc ion for activity (i.e., metallo-β-lactamases (MBL)).[10,11] In the Ambler classification there are several subtypes of serine β-lactamases resulting in hydrolysis of penicillins and cephalosporins mainly by expressing extended-spectrum β-lactamases (ESBL). Although frequently observed in the United States, ESBLs are often treated successfully with carbapenems. Of greater concern are the β-lactamases that result in

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carbapenem resistance; these can be serine based, such as Class D oxacillinase (OXA), Class A *Klebsiella pneumoniae* carbapenemase (KPC), and Class A Guiana extended-spectrum β-lactamase (GES), as well as Class B MBL-based, such as New Delhi metallo-β-lactamase (NDM), Verona Integron β-lactamase (VIM), and Imipenemase metallo-β-lactamase (IMP).

To address β-lactamase-mediated resistance in gram-negative bacteria, the combination of new and currently licensed broad spectrum β-lactamase inhibitors (BLI) with new or currently available β-lactam (BL) parent back-bones has been the most common approach to new antibiotic development in the last 15 years. However, the complexity of the individual phenotypic profiles caused by varying β-lactamase-mediated resistance remains a major challenge to clinicians. Herein, we provide a snapshot of current and promising investigational BL/BLI combination antibiotics with a focus on spectrum of activity, pharmacology, and clinical utility.

2 | GRAM-NEGATIVE RESISTANCE LANDSCAPE IN THE UNITED STATES

2.1 | Enterobacterales

ESBL prevalence in Enterobacterales has expanded globally throughout the last 10 years and accounts for ≥10% of clinical isolates of *Escherichia coli* and *K. pneumoniae* worldwide. In the United States, ESBL-producing *K. pneumoniae* significantly increased from 6.4% to 12.3% (2015–2019) and can be much higher in certain geographical regions.[12] Even though the incidence of CRE in the United States remains low (≤2%), it continues to evolve nationally with changing enzyme epidemiology.[2,13] KPC (65.5%) and NDM (11.1%) are the most prevalent carbapenemases among CRE isolated from US hospitals, with NDM seeing the steepest rise.[13] In contrast, OXA-48 like enzymes are less prevalent (4.6%) in North America when compared to the worldwide burden (19%).[2,13]

TABLE 1 Summary of Ambler classification for β-lactamases including active site and common enzymes targeted by BL/BLI antibiotics.

Ambler class	Active site	Common *β-lactamases*
A	Serine	TEM, SHV, CTX-M, ***GES***, ***KPC***
B	Metallo	***IMP, NDM, VIM***
C	Serine	AmpC, P99, PDC
D	Serine	***OXA-23, 24/40, 58,*** **OXA-48-like**

Note: Bolded enzymes indicate the carbapenemase activity.

Abbreviations: AmpC, ampicillin-resistance gene group C β-lactamase; CTX-M, Cefotaxime-Munich β-lactamase; GES, Guiana extended spectrum β-lactamase; IMP, Imipenemase metallo-β-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; OXA, Oxacillin-hydrolyzing β-lactamase; P99, *Enterobacter cloacae* cephalosporinase; PDC, *Pseudomonas*-derived cephalosporinase; SHV, sulf-hydryl variable active site β-lactamase; TEM, β-lactamase named after a patient named Temoniera; VIM, Verona Integron metallo-β-lactamase.

2.2 | Non-enterobacterales

Within *Acinetobacter baumannii*, carbapenem activity declined rapidly over the last decade with only 43.7% of isolates reported as susceptible in the United States.[14] Carbapenem-resistant *A. baumannii* (CRAB) is primarily mediated by OXA enzymes (OXA-23, 24/40, 58).[15] In *P. aeruginosa*, resistance is driven by various mechanisms including porin malfunction, efflux pumps and presence of β-lactamases, most commonly *Pseudomonas*-derived cephalosporinases (PDC).[16] Global surveillance data on *P. aeruginosa* identified 20.5% of isolates as being carbapenem resistant mainly attributed by the expression of MBLs (VIM 63.9%, IMP 10.1%, NDM 6.7%), GES (13.2%), and KPC (8.3%).[17] Fortunately, *P. aeruginosa*-producing MBL and GES-type enzymes remain very rare in the United States (≤1%).[18]

3 | CONCEPTS TO OVERCOME β-LACTAMASE-MEDIATED RESISTANCE IN GRAM-NEGATIVE BACTERIA

Small-molecule inhibitors for β-lactamases (BLI) are a common strategy to overcome resistance by preventing hydrolysis and inactivation of β-lactams. This strategy protects the active β-lactam structure and enables targeting of the transpeptidase domain of PBP, which crosslink cell wall pentapeptides during peptidoglycan synthesis.

In the last decade, novel BLIs have been developed and introduced to the market (Figure 1). All provide a broader coverage beyond class A β-lactamase inhibition compared with tazobactam, sulbactam, and clavulanic acid. Two new classes of serine BLIs with extended spectrum are cyclic boronic acid-based and diazabicyclooctane (DBO) inhibitors. The central structure of the DBO, a non-β-lactam inhibitor, is a five-membered ring containing an amide group that targets the active serine site of the β-lactamase by a carbamylation.[19] It forms a reversible, covalent adduct to the serine residue of β-lactamases.[20] The formation and lifespan of the enzyme-inhibitor complex is extremely efficient when compared with previous generations of BLIs.[21] DBOs are potent inhibitors against class A (KPC) and C (AmpC, P99, PDC) enzymes with variable activity against class D (OXA) enzymes. However, they do not inhibit class B MBLs.[19] Cyclic boronic acid inhibitors bind covalently and reversibly to β-lactamases, resulting in an enzyme-inhibitor complex that mimics the first tetrahedral intermediate in serine-based and MBL β-lactam hydrolysis.[22] Against serine-based enzymes, cyclic boronates inhibit a variety of class A, C, and D β-lactamases and represent a promising scaffold for cross-class inhibition.[22] Moreover, boronates currently in development display activity against certain MBL.[23,24]

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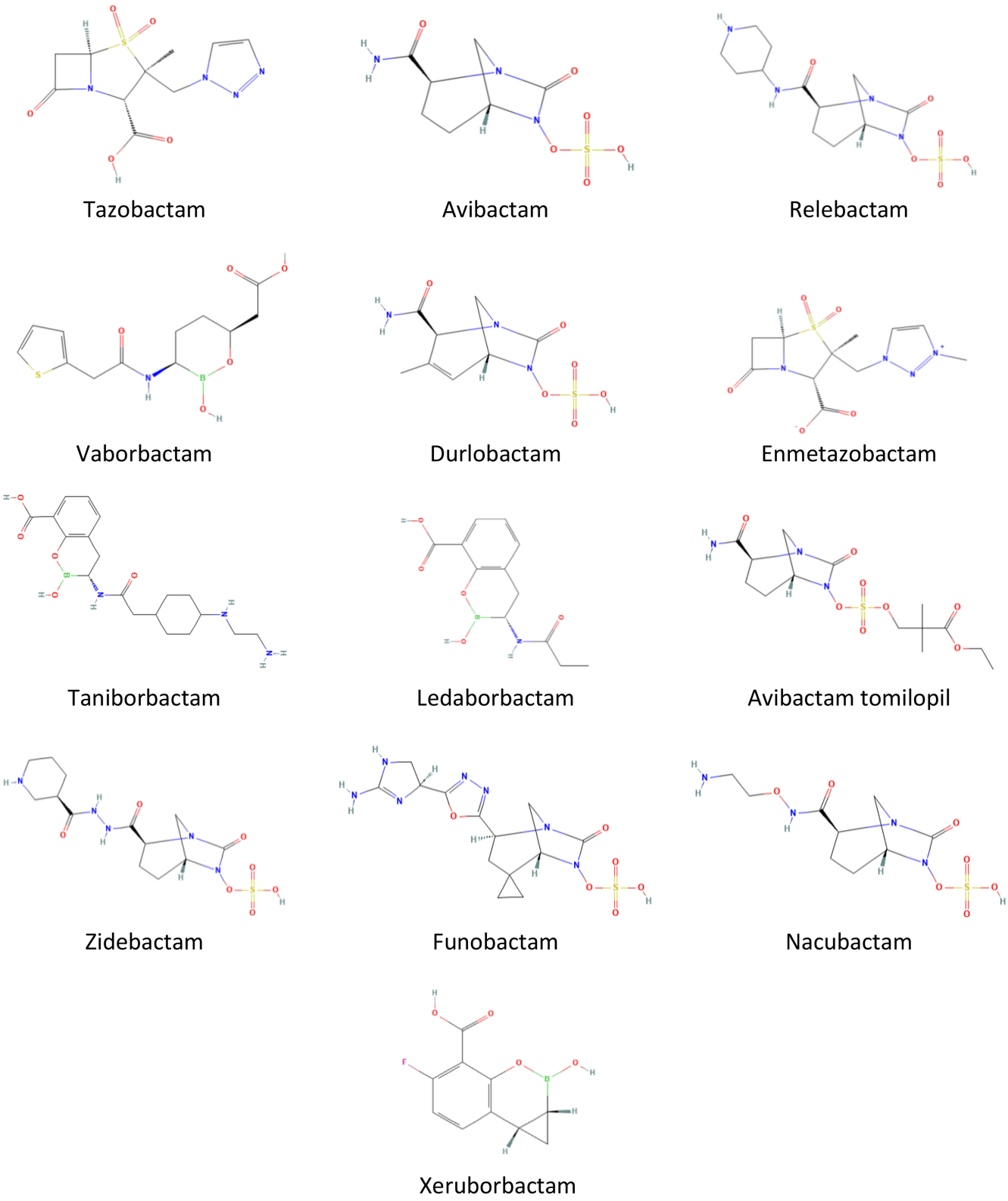

FIGURE 1 Chemical structures of currently available and investigational BLIs. Structures were created with RCSB PDB (rcsb.org) based on their isomeric SMILES.[192–204] SMILES; Simplified molecular-input line-entry system.

Additionally, some of the novel BLIs exhibit an "enhancer effect" by acting on PBP2. This effect was identified as early as 1970 when a bactericidal effect of the combination of mecillinam and ampicillin was discovered in ampicillin-resistant *E. coli*.[25] Mecillinam's high affinity to PBP2 resulted in ovoid spherical cells of Enterobacterales, *Pseudomonas* spp., and *Acinetobacter* spp. leading to lysis with the effect being amplified in the presence of ampicillin binding to PBP3.[25,26] The inactivation of multiple PBP

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targets can demonstrate synergistic effects and allow for more rapid cell wall degradation; for novel BLIs, this may be in addition to their enzyme inhibition effects.[27] Therefore, screening and developing new non-β-lactam BLIs to additionally enhance the effect of their BL partner against difficult to treat bacteria may be highly desirable.[28,29]

4 | CURRENTLY LICENSED BL/BLI ANTIBIOTICS

4.1 | Ceftolozane/tazobactam (C/T)

Ceftolozane is a cephalosporin β-lactam antibiotic targeting PBP3 with potent activity against *P. aeruginosa*, as it retains greater stability against PDCs when compared with ceftazidime. Susceptibility in *P. aeruginosa* is also generally unaffected by other resistance mechanisms including efflux pumps and porin mutations.[30,31] However, ceftolozane is prone to hydrolysis by AmpC enzymes found in Enterobacterales.[32] Although it demonstrates stability against narrow-spectrum class A enzymes (TEM-1/2, SHV-1), it is vulnerable against ESBL enzymes (TEM-3, CTX-M) and has no activity against MBL-producing strains.[31] The addition of tazobactam, a sulfone BLI, expands and/or enhances its activity for gram-negative bacteria harboring ESBL (TEM, SHV, CTM-X) enzymes.[33,34] However, C/T use in ESBL-producing Enterobacterales remains questionable as these strains often produce multiple enzymes, including AmpC, where tazobactam offers little protection and may be associated with clinical failure.[35–37] The ASPECT-NP subgroup analysis for ESBL-positive Enterobacterales did not show a significant outcome difference between C/T and meropenem for the treatment of hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP). However, since only five patients in that study had AmpC-overproducing Enterobacterales the results of the currently conducted MERINO 3 (NCT04238390) trial are awaited to inform treatment strategies.[38,39] Importantly, C/T has no activity against Gram-negatives that produce carbapenemases such as KPC, GES, OXA, and MBLs.[31,32,40]

Ceftolozane activity in the neutropenic thigh infection model was found to be best associated with the common pharmacodynamic (PD) index, the free time that concentrations remain above the minimum inhibitory concentration (MIC) for the dosing interval ($\%fT_{>MIC}$). Against *P. aeruginosa*, at least 39% $fT_{>MIC}$ was needed to achieve a 1-log kill.[41] An *in vitro* model studied tazobactam efficacy combined with ceftolozane and concluded it best correlated with $\%T_{>CT}$ with C_T being the tazobactam threshold concentration. They demonstrated that 35–75.7%$T_{>}C_T$ were sufficient for a 1-log kill of the tested Enterobacterales.[42,43] Similarly, murine thigh infection model confirmed a time-dependent dynamic with a combined $\%fT_{>MIC}$ of ≥37.5% for both drugs to achieve a 1-log reduction.

C/T is currently licensed as a 1.5 g (1 g of ceftolozane/0.5 g tazobactam) every 8 h regimen (q8h) for the treatment of adult and pediatric patients with complicated urinary tract infections (cUTI) including pyelonephritis and complicated intra-abdominal infections (cIAI) caused by several gram-negative and gram-positive organisms (i.e., *Streptococcus* spp associated with cIAI). C/T is also approved at a higher dosage (3 g q8h) in adults with HABP/VABP caused certain by gram-negative bacteria. It has become a guideline recommendation for treatment of resistant *P. aeruginosa* infections and proven successful in patients presenting with severe cases such as nosocomial pneumonia.[7,8,44,45] Of note, rare reports on resistance development in *P. aeruginosa* during therapy have emerged and mostly linked to mutations in AmpC genes and the Ω-loop where changes enhance the catalytic efficiency of β- lactamases.[46–49]

4.2 | Ceftazidime/avibactam (CZA)

Avibactam was the first approved DBO designed to demonstrate inhibition of the emerging KPC as well as class C β-lactamases.[50] Among the latter, the P99 and PDC cephalosporinases of *Enterobacter cloacae* and *P. aeruginosa* are inhibited by avibactam as well as AmpC from other Enterobacterales such as *Citrobacter freundii* or *Serratia marcescens*.[51–53]

Global resistance data reported susceptibility in 90% of CRE and 73% in carbapenem-resistant *P. aeruginosa*.[54] It should be noted that chromosomally coded PDC in *P. aeruginosa* may display different hydrolytic capacity leading to a potentially diminished activity against certain strains expressing different PDC variants; furthermore, avibactam does not prevent ceftazidime from efflux-mediated resistance. CZA demonstrated MIC_{50} and MIC_{90} of 2/4 and 8/4 mg/L against meropenem-resistant *P. aeruginosa*, thus resulting in susceptibility >90% at the susceptibility breakpoint of 8/4 mg/L.[55,56] Against class D OXA enzymes, only OXA-48-like enzymes are sufficiently inhibited by avibactam in *in vitro* and *in vivo* studies; when combined with low hydrolytic potential for ceftazidime, CZA becomes an attractive option for isolates producing OXA-48-mediated resistance.[51,57] The MIC_{50} and MIC_{90} in OXA-48 producing *K. pneumoniae* was 2/4 and 4/4 mg/L, respectively, with 99% susceptibility.[58,59] Also, when OXA-48 resistance was paired with other mechanisms (e.g. ESBL, transferrable AmpCs, porin alterations), CZA still demonstrated susceptibility rates >99%.[59] However, there are reports on emergence of resistance during CZA therapy in KPC-2- and -3-producing organism due to mutations in the Ω-loop that allow trapping of ceftazidime and prevention of avibactam binding.[60,61]

Human simulated profiles of CZA in hollow-fiber and mice models revealed that antibacterial efficacy of the combination is linked to the $\%fT_{>MIC}$ profile.[62] Murine lung and thigh infection models more precisely defined $\%fT_{>MIC}$ in epithelial lining fluid (ELF) and plasma to be ≥20% and ≥60%, respectively, for activity against *P. aeruginosa* and Enterobacterales when using CZA doses equivalent to 2.5 g (2 g/0.5 g) q8h as a 2-h infusion.[63,64] The driver for avibactam PD was found to be the time that avibactam exceeded a concentration threshold (C_T) $fT > C_T$.[65,66] This is supported by outcome data from critically ill patients achieving the joint target of $\%fT_{>MIC}$ for ceftazidime and $fT > C_T$ (C_T of 4 mg/L) for avibactam.[67–69]

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CZA is currently approved in adults and pediatrics (>3 months) for the treatment of cIAI, cUTI, and HABP/VABP caused by gram-negative bacteria. It is used in particular in the treatment of KPC- and OXA-48-expressing CRE as well as carbapenem-resistant *P. aeruginosa*. Moreover, it has been successfully used in cases with *Burkholderia cepacia complex* infections.[70,71] For the treatment of MBL-positive infections, such as NDM and *Stenotrophomonas maltophilia*, the combination of CZA with aztreonam has proven a valuable option (see Section 5.1 aztreonam/avibactam for details).[72]

4.3 | Imipenem/cilastatin/relebactam (IMI/REL)

Relebactam is a non-β-lactam DBO that offers broad spectrum activity against a wide range of β-lactamases. This mechanism demonstrates activity against class A (TEM, SHV, CTX-M, KPC) and C (AmpC, PDC, P99) β-lactamases expressed by various Enterobacterales, as well as *P. aeruginosa*.[73–77] GES (2, 5, 19, 20) type class A and B MBL enzymes are not inhibited[74,78–80] and it does have limited activity on class D β-lactamases such as OXA-48.[81] Relebactam potentiated the activity of imipenem against imipenem non-susceptible *P. aeruginosa*.[81] As imipenem is stable against PDC this effect can be explained as follows: in the presence of PDC, OprD is downregulated resulting in resistance due to porin loss.[82] With the inhibition of PDC by relebactam, OprD porins are still present and allow imipenem to enter the bacterial cell.[83]

Surveillance data from US hospitals for IMI/REL demonstrated the overall susceptibility for Enterobacterales of 98.9%, including KPC-producing strains.[54] Difficult to treat Enterobacterales demonstrating carbapenem resistance resulted in a susceptibility rate of 82.4%; this lower susceptibility was due to presence of MBLs and OXA-48-like enzymes.[84] For *P. aeruginosa*, overall MIC_{50} and MIC_{90} were 0.25/4 and 1/4 mg/L with 97.3% of US isolates defined as susceptible. However, against C/T- and ceftazidime-resistant *P. aeruginosa*, susceptibility rates were 45%–65%.[85] Among GES-expressing carbapenem-resistant *P. aeruginosa*, IMI/REL was active against 13% of the isolates with MIC_{50} and MIC_{90} of 16/4 and >16/4 mg/L.[86]

Imipenem PD has been described previously and was reinvestigated in the presence of relebactam.[87] Maximum antibiotic effect of the combination best related to the target $\%fT_{>MIC}$ for imipenem, with 40% $fT_{>MIC}$ required for 1–2 log kill. For relebactam, murine infection models including thigh and lung as well as the *in vitro* hollow fiber model reported that free area under the curve over 24 h to MIC ($fAUC/MIC_{24}$) was the PD target for efficacy with values between 7 and 8 mg*h/L in *K. pneumoniae* and *P. aeruginosa* for 2-log kill.[88–90] A population pharmacokinetic (PK) analysis of healthy volunteers and patients was performed with a joint target ($fAUC_{0-24}/MIC$ ≥8 and imipenem ≥40% $fT_{>MIC}$[88]) to develop the eventually approved dosing regimen of 1.5 g (0.5 g imipenem, 0.5 g cilastatin, 0.5 g relebactam) q6h as a 0.5-h infusion.[91]

IMI/REL was studied in the RESTORE-IMI 2 phase 3 trial which included two third of patients in the ICU with mostly *K. pneumoniae*- and *P. aeruginosa*-positive HABP/VABP.[92] It is approved by the United States Food and Drug Administration (FDA) for the use in HABP/VABP, cUTI, and cIAI caused by various susceptible gram-negative bacteria.[93] Clinically, IMI/REL is an option for KPC-producing CRE and non-carbapenemase producing *P. aeruginosa*, where it may serve to spare other reserved antibiotics (e.g. cefiderocol, C/T). However, due to higher resistance rates across non-KPC multidrug resistant mechanisms, susceptibility testing is recommended.

4.4 | Meropenem/vaborbactam (MVB)

Vaborbactam is the first approved cyclic boronic acid BLI. Vaborbactam provides inhibitory effects on diverse class A (KPC, SHV, TEM, and CTX-M) and C (AmpC, P99) carbapenemases.[94] However, there is no effect on class B MBL and D (OXA) carbapenemases.[57,81,95] US susceptibility data for multi-drug resistant Enterobacterales showed overall MIC_{50} and MIC_{90} of 0.03/8 and 0.12/8 mg/L with 99.1% susceptibility for MVB. In the carbapenem-resistant subgroup, MIC_{50} and MIC_{90} were 0.03/8 and 2/8 mg/L (93.2% susceptibility) with KPC-producing isolates as low as 0.03/8 and 0.5/8 mg/L and a 98.9% susceptibility.[96] This study also reported 89.7% of non-carbapenemase-producing CRE susceptible to MVB (MIC_{50} 2/8 mg/L, MIC_{90} 8/8 mg/L). However, these results should be cautiously interpreted as the Clinical and Laboratory Standards Institute (CLSI) currently states susceptibility breakpoints of 4/8 mg/L for MVB and 1–2 mg/L for meropenem alone.[97] This knowledge is of significant importance, as MVB may be reported susceptible despite its lack of activity against Enterobacterales producing OXA-48-like enzymes, a phenomenon already reported in a global surveillance study (susceptibility rates: meropenem 25% vs. MVB 47%).[59] Moreover, vaborbactam does not potentiate the effect of meropenem alone in *P. aeruginosa* (MIC_{50} and MIC_{90} > 16/8 mg/L).[86] Carbapenem resistance in *P. aeruginosa* isolates are caused by a number of mechanisms that are not impacted by vaborbactam such as porin loss, efflux pumps, and MBLs.[98]

Meropenem's PD has been described previously with $\%fT_{>MIC}$ to be the best predictor for antimicrobial activity.[99] Hence, animal models suggest 40% $fT_{>MIC}$ to be achieved to maximize its bactericidal effect.[100] For vaborbactam, $fAUC_{24h}$/MVB MIC best described the antibacterial activity in a murine thigh infection and a hollow fiber model.[101] For stasis and 1-log kill, $fAUC_{24h}$/MIC of 9–12 and 18–38 were required, respectively.[19] With MVB clinical breakpoint for Enterobacterales of 4/8 mg/L, the necessary exposure for optimal PD (1-log kill) translates in a vaborbactam $fAUC_{24h}$ > 152 mg*h/L. Data from population pharmacokinetic models from two Phase 3 clinical trials showed that vaborbactam $fAUC_{24h}$ on day one of 776 ± 49 mg*h/L was achieved.[102] Based on that MVB 4 g (2 g meropenem/2 g vaborbactam) q8h as a 3-h infusion is currently indicated by the FDA for the treatment of cUTI including pyelonephritis caused by susceptible gram-negatives.[103] Although the primary clinical utility of MVB remains against KPC-producing CRE, activity combinations with other β-lactams may offer additional areas of utilization as highlighted by a recent review.[104,105]

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4.5 | Sulbactam/durlobactam (SUL/DUR)

Sulbactam is an older BLI that inhibits class A β-lactamases, but with intrinsic β-lactam antibacterial effect against *A. baumannii* infections due to its binding and inhibition of PBP1a/b and PBP3.[106] Durlobactam is a novel DBO BLI derived from its predecessor avibactam. It inhibits class A β-lactamases (KPC, SHV, TEM, CTX-M) and C (AmpC, P99, PDC) as well as a variety of class D OXA β-lactamases (OXA-10, 23, 24/40, 48) that are prevalent in CRAB.[107–110] Against carbapenem-resistant *A. baumannii*, SUL/DUR MIC_{50} and MIC_{90} were 1/4 mg/L and 2/4 mg/L, respectively, with 96.9% susceptibility reported based on the current breakpoint of ≤4/4 mg/L.[111] Currently, only MBLs produced by *A. baumannii* escape activity from durlobactam.

Recent murine lung and thigh infection models provided additional data to the PK/PD index of sulbactam against *A. baumannii*. The index best associated with activity in the thigh infection model was $\%fT_{>MIC}$ with a magnitude of 21% for stasis and 43.6% for a 2-log reduction, respectively.[112] These data were supported by *in vitro* hollow fiber studies and confirmed in *in vivo* thigh and lung infection models, where $fAUC_{0-24}$/MIC of 16–33.4 was required for 2-log reductions against multiple *A. baumannii* isolates.[113] This translates into required clinical AUCs of at least 64–133 mg*h/L for DUR. Pharmacokinetic data from clinical trials revealed 24 h AUCs of 471 ± 270 mg*h/L for patients with a creatinine clearance (CrCl) 90–130 mL/min.[114] To allow for a joint target of >50% $fT_{>MIC}$ sulbactam and sufficient $fAUC_{0-24}$/MIC for durlobactam, SUL/DUR is dosed in a fixed ratio of 2 g/1 g every 6 h as a prolonged infusion over 3 h.[115]

The combination of SUL/DUR as a 3-h infusion of 1 g sulbactam/1 g durlobactam q6h was recently approved by the FDA based on the non-inferiority trial against colistin-based CRAB treatments in combination with imipenem-cilastatin.[116] The label currently includes the treatment of HABP/VABP caused by susceptible *A. baumannii-calcoaceticus* complex.[115] Therefore, it should be noted that additional antimicrobial coverage is needed when treating polymicrobial infections that include *A. baumannii*.

Despite its focused use for serious CRAB infections, there may be potential for use against other CRO. For example, a study demonstrated *in vitro* susceptibility for SUL/DUR in >87% of the tested *Burkholderia* spp as well as inhibition of PenA1 and PenI β-lactamases.[117] Similarly, *in vitro* time-kill studies indicate a potential to restore cefepime activity in formally cefepime-resistant *P. aeruginosa* presumably by additive effects on PBP1 and PBP3.[118] Further studies are needed to investigate utility outside of *A. baumannii* infections.

4.6 | Cefepime/taniborbactam (FEP/TAN)

Taniborbactam (formerly VNRX-5133) is a boron-based bicyclic BLI with a broad spectrum that inhibits all four Ambler classes of β-lactamases.[23] Combined with cefepime (at a fixed concentration of 4 mg/L) it restored cefepime's activity against Enterobacterales with ESBL, KPC, AmpC, and OXA-48 enzymes. FEP/TAN has recently shown MIC_{50} of 1/4 and MIC_{90} of 4/4 mg/L for KPC-producing Enterobacterales including ESBLs with 84.1% of isolates being inhibited at an MIC ≤2/4 mg/L. OXA-48-positive isolates were highly susceptible (93.1% at MIC ≤2/4 mg/L) with FEP/TAN MIC_{50} and MIC_{90} of ≤0.5/4 and 2/4 mg/L, respectively.[119] It also revealed promising activity against Enterobacterales expressing MBL with MIC_{50} and MIC_{90} data ranges of 0.5–1/4 and 2–8/4 mg/L.[119,120] However, it was found to be inactive against IMP MBL.[121] It also demonstrated less pronounced *in vitro* potentiation of cefepime against NDM- and VIM-positive non-Enterobacterales such as *P. aeruginosa* (MIC_{50} andMIC_{90}: 16/4 and 32/4 mg/L)[122] as well as *A. baumannii* with OXA and NDM carbapenemases, presumably due to presence of additional resistance mechanisms (e.g., efflux pumps, etc).[121] On the other hand, time-kill studies resulted in 3-log kill of NDM-1-producing *K. pneumoniae* and VIM-2-producing *P. aeruginosa*.[120] Despite its promising activity there are already first reports on NDM-1 and NDM-9 isolates with resistance to FEP/TAN.[123,124] *In vitro* susceptibility testing of *S. maltophilia* strains (MIC 2–16/4 mg/L) and results from murine infections models point towards inhibition of the cefepime-hydrolyzing L2 enzyme, but not the L-MBL.[121,125]

Finally, the addition of taniborbactam reduced the cefepime MIC_{50} and IMIC$_{90}$ to 8/4 and 32/4 mg/L against clinical *Burkholderia cepacia complex* and *Burkholderia gladioli* strains from cystic fibrosis patients indicating a potential use against these inherently multidrug-resistant isolates.[126]

Cefepime PD are best described by $\%fT_{>MIC}$.[127] When taniborbactam PK/PD index was investigated, $fAUC_{0-24}$/MIC was the best descriptor for efficacy end points. The murine pneumonia model highlights the need for $fAUC_{0-24}$/MIC of 4.03 for a 1-log kill in Enterobacterales (expressing CTX-M, KPC, and OXA-48) and 3.02 for *P. aeruginosa* (AmpC producing).[128] The murine thigh infection model revealed $fAUC_{0-24}$/MIC thresholds of 2.64 and 0.46 for Enterobacterales and *P. aeruginosa*, respectively.[129] Furthermore, the novel combination provided robust killing of ESBL-producing Enterobacterales, *P. aeruginosa*, and *S. maltophilia* when mimicking human plasma profiles in the murine cUTI model.[125] FEP/TAN dosed with 2 g/0.5 g over a 2-h infusion every 8 h was investigated in phase I/II trials and recently proved superiority against meropenem for the treatment of cUTI and pyelonephritis (CERTAIN-1).[130–132] It is now awaiting FDA approval for the indication of cUTI and acute pyelonephritis (AP) caused by multidrug-resistant gram-negative bacteria. Its spectrum of activity will provide the first approved BL/BLI treatment option for MBLproducing isolates.

4.7 | Cefepime/enmetazobactam

Enmetazobactam (formerly AAI-101) is an *N*-methylated derivative of tazobactam representing the class of β-lactam-containing BLIs (penams). The addition of a methyl-group results in a compound with neutral charge and enhanced potency as it penetrates

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the gram-negative cell wall with a higher rate.[133] It has activity against a broad range of class A β-lactamases (SHV, TEM, and CTX-M-14/15).[134]

A joint US and European surveillance study from isolates recovered from serious health care-associated infections tested cefepime/enmetazobactam (fixed enmetazobactam of 8 mg/L) against various Enterobacterales. The addition of enmetazobactam lowered the MIC_{90} to 0.25/8 mg/L compared with cefepime alone (32 mg/L) and resulted in a cumulative susceptibility (at 8 mg/L cefepime representing the CLSI susceptible-dose dependent (SDD) category) of 98.1%. *E.coli* and *K.pneumoniae* isolates with ESBL genotype revealed MIC_{50} and MIC_{90} of 0.06/8 and 0.12/8 as well as 0.12/8 and 1/8 mg/L, respectively. Applying the CLSI cefepime breakpoint of 8/8 mg/L resulted in 99.1% and 92.2% susceptibility for ESBL-producing *E.coli* and *K.pneumoniae*.[135] Overall, the MIC_{50}/MIC_{90} were lower than piperacillin/tazobactam and similar to meropenem, which suggests cefepime/enmetazobactam may be a carbapenem-sparing option in ESBL-producing Enterobacterales. Cefepime/enmetazobactam also permits activity against Enterobacterales expressing class C (AmpC) and D (OXA-48) enzymes due to cefepime's stability against hydrolysis from these enzymes.[133] Sufficient activity against KPC-expressing strains remains controversial: enmetazobactam demonstrated *in vitro* inhibition of KPC in one study[134]; however, KPC-expressing *K.pneumoniae* demonstrated high MIC_{50} and MIC_{90} with values of 16/8 and >64/8 mg/L translating to only 42.2% susceptibility (8/8 mg/L cefepime).[135]

Murine neutropenic lung and thigh infection models indicate that time dependent indices are predictive for cefepime and enmetazobactam's efficacy.[136,137] It was found that 44% $fT_{>2mg/L}$ of enmetazobactam combined with 40%–60% $fT_{>MIC}$ for cefepime result in a 1-log kill for ESBL-producing *K.pneumoniae* in the thigh infection model.[137] PD evaluation in the lung model considered 20% $fT_{>MIC}$ for cefepime along with 20% $fT_{>2mg/L}$ for enmetazobactam to be sufficient for a 2-log kill in ELF.[136] It was recently granted FDA approval in 2024 for treating cUTI with a dose of 2 g cefepime/0.5 g enmetazobactam q8h infused over 4 h based on the phase III trial against the comparator piperacillin/tazobactam.[138] Both microbiological eradication and clinical cure at the end of treatment were in favor of cefepime/enmetazobactam (combined primary outcome achieved in 79.1% versus 58.9%, diff: 21.2%, 95% confidence interval, 14.3%–27.9%).

5 | PIPELINE BL/BLIs

5.1 | Aztreonam/avibactam (ATM/AVI)

Aztreonam is a monobactam not hydrolysed by class B MBL and therefore an attractive candidate for treating infections by gram-negative isolates expressing MBL. Unfortunately, these isolates of interest frequently co-produce class A or AmpC-type β-lactamases leaving few susceptible to aztreonam alone.[139] Avibactam is a non-β-lactam BLI with activity against class A (TEM, SHV, and CTX-M, KPC), C (AmpC, P99), and OXA-48 β-lactamases.[51] Surveillance data of isolates from US hospitals result in MIC_{50} and MIC_{90} of ≤0.25/4 and 0.5/4 mg/L for CRE.[13] MIC_{50} and MIC_{90} remained low when looking at the subgroup of extensively drug-resistant (XDR) and MBL (NDM, VIM, IMP)-expressing isolates with values of 0.25/4 and 0.5/4 mg/L and susceptibility ≥99% at 8/8 mg/L.[13] Against *P.aeruginosa* ATM/AVI use may be limited, as global data revealed MICs above the breakpoint of 8 mg/L for the majority of strains regardless of the presence of MBLs.[140] Finally, ATM/AVI has activity against most *S.maltophilia* given avibactam inhibits the Class A L2 β-lactamase, allowing aztreonam, which is stable to the L1 MBL, to bind to its active site.[141]

Hollow fiber models with NDM-producing *K.pneumonia* and *E.coli* strains resulted in rapid and sustained bacterial kill when CZA (6 g/1.5 g/24 h) was combined with aztreonam (6–8 g/24 h). Prolonged and simultaneous infusion were needed against tested NDM isolates. Moreover, using 8 g/24 h aztreonam further enhanced the performance of the combination.[142] Hence, this study supports $\%fT_{>MIC}$ being the PK/PD index for ATM/AVI. Additionally, early studies in the neutropenic thigh infection model showed that maximal efficacy was seen with ≥65% $fT_{>MIC}$ for Enterobacterales including MBL-producing strains. Notably, a human aztreonam dose of 8 g/24 h was mimicked whereas current clinical trials investigate 6 g/24 h.[143,144]

ATM/AVI efficacy and safety is currently being evaluated in clinical trials for serious infections due to gram-negative bacteria including MBL-producing strains. Trials are run against comparators such as meropenem ± colistin (NCT03329092) or best available therapy (NCT05639647, NCT03580044). Recently, ATM/AVI was approved by the European Medicine Agency.[145] Until licensed in the United States, CZA combined with aztreonam will remain a viable option for the treatment of infections caused by MBL-positive isolates guided by novel susceptibility testing methods.[146] This is supported by clinical data suggesting a therapeutic advantage compared to other active antibiotics (e.g. polymyxins, aminoglycosides).[147,148] Moreover, case reports support the effectiveness of CZA combined with aztreonam in infections with *S.maltophilia*[149–151] and diverse MBL-expressing Enterobacterales including *K.pneumoniae*, *Citrobacter* spp., and *Enterobacter* spp.[152–157]

5.2 | Ceftibuten/ledaborbactam

Ledaborbactam (formerly VNRX-5236) and it is orally bioavailable prodrug ledaborbactam etzadroxil (VNRX-7145) are boronic acid based and currently in development with ceftibuten for oral treatment of ESBL and serine-carbapenemases. This BL/BLI has broad spectrum activity against Class A, C, and D classes including KPC-2 and OXA-48.[158] Unfortunately, activity against class B MBL is lacking. Ceftibuten was chosen as a partner due to its lowest MICs when combined with ledaborbactam against strains producing ESBL, KPC, AmpC, and OXA-48 enzymes.[158] Overall MIC_{50} and MIC_{90} were 0.06–1/4 and 0.12–2/4 mg/L for clinical Enterobacterales.[158–160] Global surveillance data

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demonstrated that ledaborbactam restored ceftibuten activity in 86% of ceftibuten-resistant Enterobacterales.[161] Within ESBL-producing species (CTM-X, SHV, and KPC), MIC_{50} and MIC_{90} were 0.06/4 and 0.25/4 mg/L with 98% of isolates being inhibited at ≤8/4 mg/L.[161]

Similar to other cephalosporins ceftibuten's efficacy correlates well with the achieved $\%fT_{>MIC}$. An *in vivo* model revealed exposure-response variability in between different strains with an composite $\%fT_{>MIC}$ of 39% and 67% for stasis and 1-log kill, respectively.[162] The PD of ledaborbactam in the presence of ceftibuten was first described in the murine thigh infection model.[163] $fAUC_{0-24}$/MIC for ledaborbactam was the best predictor for antibacterial activity. Hence, a median ledaborbactam $fAUC_{0-24}$/MIC of 3.59 achieved bacteriostasis against various Enterobacterales albeit there was notable variability on the individual isolate basis. Phase I studies (NCT05488678, NCT04243863, NCT04877379, and NCT05527834) on ceftibuten and ledaborbactam pharmacokinetics are completed and give hope that an oral treatment option for ESBL, KPC, and OXA-48-producing isolates will be available.[164]

5.3 | Ceftibuten/avibactam

Recently an oral formulation of the prodrug avibactam tomilopil (ARX-1796) was developed using a novel method to protect the charged sulfate moiety of the DBO by synthesizing an 0-neopentyl ester.[165] It is currently in early phase development as an oral treatment partnered with ceftibuten to treat cUTI infections including AP. The combination provides antimicrobial activity against class A (ESBL, KPC), C (AmpC), and D (OXA-48-like) β-lactamase producing Enterobacterales. *In vitro* activity has been shown against a variety of urogenic Enterobacterales in two global surveillance program analyses.[166,167] Ceftibuten/avibactam MIC_{50} for ESBL and KPC-producing isolates were 0.03/4 and 0.12/4 mg/L with MIC_{90} of 0.25/4 and 0.5/4 mg/L, respectively.[166,167] Of these isolates ≥99% were inhibited at a ceftibuten/avibactam concentration of ≤8/4 mg/L.[166,167] Chromosomally harbored and acquired AmpC-producing isolates showed a MIC_{50} and MIC_{90} of 0.06–0.12/4 and 1–4/4 mg/L with 92% and 99% of the isolates being inhibited (≤8/4 mg/L). Moreover, the novel combination inhibited 96% of OXA-48-like producing isolates with an MIC_{50} of 0.25/4 and MIC_{90} of 2/4 mg/L.[166] The combination is currently Phase I trials (NCT05554237) and if approved will provide another oral option for a variety of β-lactamases (ESBL, KPC, and OXA-48).

5.4 | Cefepime/zidebactam

Zidebactam (formerly WCK5107) is a novel DBO which is currently investigated in combination with cefepime (WCK5222). It provides dual activity as a BLI and as a direct antibacterial exerting an enhancer effect via PBP2 targeting β-lactams.[75] Cefepime alone provides AmpC stability, targets PBP3, and demonstrates high PBP2 affinity in Enterobacterales, but low PBP2 affinity in *P. aeruginosa*. Zidebactam combined with cefepime allows for enhanced cell inhibition activity and is stable against the hydrolysis of a wide range of β-lactamases including AmpC, ESBL, KPC, and OXA-48.[168] An analysis of worldwide collected gram-negative isolates resistant to carbapenems revealed that cefepime/zidebactam inhibited 97.8% (at ≤8/8 mg/L) of CRE (MIC_{50} 0.5–1/8 and MIC_{90} 2–8/8 mg/L).[169,170] It is noteworthy that zidebactam itself does not inhibit MBLs intrinsically but demonstrates activity against MBL-producing isolates by its complementary PBP-binding capability.[168,171] Thus, this combination inhibited 94.8% (at ≤8/8 mg/L) of MBL-producing Enterobacterales with an MIC_{50} and MIC_{90} of 0.5/8 and 4/8 mg/L. However, MBL positive *P. aeruginosa* revealed higher MIC_{50} and MIC_{90} of 8/8 and 16/8 mg/L.[170] For NDM-producing *E. coli* strains resistant to ATM/AVI a low MIC_{90} of 0.25/4 mg/L for cefepime/zidebactam was observed.[172] Activity against meropenem-resistant *A. baumannii* was less than other organisms with only 34% of strains having a MIC ≤8/8 mg/L.[173]

As a cephalosporin cefepime alone exhibits time-dependent bactericidal activity with 50%–70% $fT_{>MIC}$ being the target for efficacy.[127] Murine thigh and lung infection models for cefepime/zidebactam showed that $\%fT_{>MIC}$ to achieve a 1-log kill is only 31%–39% including MBL-producing Enterobacterales and CRAB.[174–176] The *in vivo* activity of cefepime was augmented by the addition of zidebactam also expressed by the reduced pharmacodynamically needed exposures compared to cefepime monotherapy. These findings are promising and are supported by early case reports of patients being successfully treated with compassionate use of cefepime/zidebactam for NDM-producing *P. aeruginosa*.[177–179] Cefepime/zidebactam is currently being studied in a phase III trial for the treatment of cUTI and AP (NCT04979806).

5.5 | Xeruborbactam combinations

Xeruborbactam (QPX7728) is a cyclic boronic acid BLI covering an ultra-broad spectrum of enzymes. It exhibits activity against class A (CTX-M, KPC, SHV, and TEM), C (AmpC, PDC, and P99), and D (OXA-23, OXA-24/40, and OXA-58) serine β-lactamases.[110] Importantly, xeruborbactam showed considerable potency against clinically important class B enzymes NDM and VIM but with a somewhat lower extent to IMP-1 and IMP-26 enzymes.[75] It restored meropenem activity in CRE (xeruborbactam fixed at 8 mg/L) with MIC_{50} and MIC_{90} of ≤0.03–0.06/8 and 0.25–0.5/8 mg/L with 99.3%–99.6% of the isolates being susceptible at the breakpoint of 8 mg/L for 2-g meropenem q8h by a 3-h infusion.[180,181] Notably, xeruborbactam combined with meropenem showed activity against the subgroup of CRE harboring defective porins (OmpK36) with MIC_{50} of 0.125/8 and MIC_{90} of 1/8 mg/L and 98.8% susceptibility (≤8/8 mg/L).[180] Against MBL-producing (NDM, VIM) Enterobacterales, xeruborbactam restored meropenem activity with MIC_{50} and MIC_{90} of ≤0.03/8 and 1/8 mg/L with 98.7% of tested isolates being inhibited.[181] In *A. baumannii* the addition of xeruborbactam to meropenem resulted in MIC_{50} of 0.5–2/8 mg/L and MIC_{90} of 2–8/8 mg/L dependent on the present OXA- enzyme

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TABLE 2 Summary of spectrum of activity for currently available and investigational (italicized) new BL/BLI combination antibiotics and potential clinical utility.

Drug	Class A	Class B	Class C	Class D	Chemical Class of BLI	Clinical utility
Ceftolozane/tazobactam	TEM, SHV, CTX-M	–	–	–	β-lactam	• Carbapenem-resistant *P. aeruginosa*
Ceftazidime/avibactam	TEM, SHV, CTX-M, KPC	–	AmpC, P99, PDC	OXA-48	DBO	• KPC, OXA-48-producing CRE • Carbapenem-resistant *P. aeruginosa*
Imipenem/relebactam	TEM, SHV, CTX-M, KPC	–	AmpC, P99, PDC	–	DBO	• KPC-producing CRE • Non-carbapenemase-producing *P. aeruginosa*
Meropenem/vaborbactam	TEM, SHV, CTX-M, KPC	–	AmpC, P99, PDC	–	Boronic acid	• KPC-producing CRE • *P. aeruginosa* (no activity beyond meropenem alone)
Sulbactam/durlobactam[a]	TEM, SHV, CTX-M, KPC	–	AmpC, P99, PDC	OXA-10, 23, 24/40, 48	DBO	• CRAB
Cefepime/taniborbactam	TEM, SHV, CTX-M, KPC	NDM, VIM	AmpC	OXA-48	Boronic acid	• KPC, OXA-48, or MBL-producing CRE
Cefepime/enmetazobactam	SHV, TEM, CTX-M, (±KPC)[b]	–	AmpC	OXA-48	β-lactam	• ESBL-producing Enterobacterales
Aztreonam/avibactam	TEM, SHV, CTX-M, KPC	NDM, VIM, IMP	AmpC, P99	OXA-48	DBO	• KPC, OXA-48, or MBL-producing CRE • *S. maltophilia*
Ceftibuten/ledaborbactam	TEM, SHV, CTX-M, KPC	–	AmpC	OXA-48	Boronic acid	• ESBL-producing Enterobacterales • KPC, OXA-48-producing CRE
Ceftibuten/avibactam tomilopil	TEM, SHV, CTX-M, KPC	–	AmpC	OXA-48	DBO	• ESBL-producing Enterobacterales • KPC, OXA-48-producing CRE
Cefepime/zidebactam	TEM, SHV, CTX-M, KPC	+[d]	AmpC	OXA-48	DBO	• KPC, OXA-48, or MBL-producing CRE
Xeruborbactam	TEM, SHV, CTX-M, KPC	NDM, VIM (±IMP)	AmpC, P99, PDC	OXA-23, OXA-24/40, 58	Boronic acid	• KPC-producing CRE • AmpC-producing Enterobacterales and *P. aeruginosa* • MBL and OXA-expressing CRE
Imipenem/funobactam	TEM, SHV, CTX-M, KPC	–	AmpC, PDC	OXA-20/40	DBO	• ESBL and KPC-producing CRE • CRAB
Nacubactam	TEM, SHV, CTX-M, KPC	+[c]	AmpC, P99, PDC	OXA-48	DBO	• KPC-producing CRE • AmpC-producing Enterobacterales and *P. aeruginosa* • MBL harboring CRE if combined with aztreonam

Abbreviations: BL, β-lactamase; BLI, β-lactamase inhibitor; CRAB, carbapenem resistant *A. baumannii*; CRE, carbapenem resistant Enterobacterales; DBO, diazabicyclooctane; MBL, metallo β-lactamase.

[a]Durlobactam β-lactamase activity only.

[b]Controversial data.

[c]In vitro synergy with aztreonam, needs to be further specified.

[d]To be further specified.

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(OXA-23, OXA-72, OXA-24, OXA-58, OXA-239) with susceptibility rates ≥90%.[182] Against *P. aeruginosa* (resistant to meropenem, C/T, CZA) xeruborbactam inhibited a higher portion of the strains at their susceptibility breakpoint compared with the partner β-lactam.[183] Therefore, partnering xeruborbactam with various parenteral and oral β-lactams seems a promising approach to target different resistance scenarios. As such, *in vivo* murine thigh infection models demonstrated xeruborbactam's potential as a partner to various β-lactams (e.g. cefepime, ceftolozane, meropenem, aztreonam) as all combinations allowed for 1-log bacterial killing of multidrug-resistant *K. pneumoniae* strains.[184]

The intravenous xeruborbactam formulation is currently studied in phase I trials either alone or combined with another β-lactam (QPX2014) to investigate drug–drug interactions (NCT05072444) as well as its pharmacokinetics and safety profile (NCT04380207). Additionally, phase I studies for the oral prodrug (NCT06157242, NCT06157242) are scheduled. Overall, xeruborbactam could be an intravenous and oral partner BLI for a variety of BL, offering a therapeutic option for a variety of MBL CRO as well as CRAB.

5.6 | Imipenem/cilastatin/funobactam

Funobactam (also known as XNW4107), a DBO BLI without intrinsic activity when used in monotherapy, is currently under development in combination with imipenem/cilastatin. It exhibits activity against Class A, C, and D β-lactamases including OXA-20/40-like enzymes frequently present in CRAB.[185] Susceptibility assessments demonstrated MIC_{50} and MIC_{90} of 2/8 and 8/8 mg/L (funobactam fixed to 8 mg/L) against imipenem-resistant *A. baumannii* with susceptibility rate of 57.5% when applying the CLSI breakpoint of imipenem (≤2/8 mg/L). Imipenem-resistant *K. pneumoniae* had MIC_{50} of 0.25/8 and MIC_{90} of 2/8 mg/L with 88.9% susceptibility (≤1/8 mg/L).[185]

The exposure response relationship of imipenem/cilastatin/funobactam was investigated in the neutropenic thigh infection model for a selection of *A. baumannii* (OXA-23/51 like) and *K. pneumoniae* (KPC, CTX-M, and SHV). A novel index of $(\%fT_{>}C_T)$/MIC with C_T being set to a funobactam concentration of 1 mg/L best described the *in vivo* efficacy. For *A. baumannii* a 1-log reduction was associated with a median $(\%fT > C_T)$/MIC of 9.82 whereas the tested *K. pneumoniae* isolates only reached stasis at 55.73%.[186] As therapeutic options against CRAB are limited, these data support further endevours to close this medical need. Imipenem/cilastatin/funobactam is currently being studied in two phase III clinical trials for the treatment of bacterial pneumonia (NCT05204563) and cUTI including AP (NCT05204368).

5.7 | Nacubactam combinations

Nacubactam (formerly RG6080/OP0595) is a DBO with inhibition capability against class A ESBL, KPC, and C (AmpC) β-lactamase enzymes.[187–189] In addition, it exhibits affinity towards PBP2 for many gram-negative species and shows intrinsic activity against Enterobacterales. This allows it to exert a direct antibacterial effect and an enhancer mechanism by potentiating a partner BL which acts on PBP3.[29] As such, the addition of nacubactam (fixed at 4 mg/L) to various BLs (piperacillin, cefepime, aztreonam) in OXA-48-producing Enterobacterales revealed significant reductions in MICs versus the unprotected compounds.[189] In particular, its enhancer characteristics are likely to contribute to its potentiation of BLs against OXA-48.[190] The same hypothesis as a triple active DBO is utilized to explain nacubactam's potential to lower meropenem, cefepime, and aztreonam MIC significantly in MBL producers. Overall, 84.8% and 90% of MBL-expressing isolates were susceptible at meropenem and cefepime MIC of 8 mg/L with a fixed nacubactam concentration of 4 mg/L. However, aztreonam/nacubactam was more universally potent against MBLs (>99% susceptibility) mainly due to aztreonam stability against MBL and nacubactam's enhancer effect.[191] Dependent on its partner BL, nacubactam could be utilized for KPC, AmpC, as well as MBL-producing CRE.

6 | CONCLUSION

Increasing rates of carbapenem resistance among gram-negative organisms continues to be a global threat. During the last decade several novel BL/BLI combinations for the treatment of these difficult to treat bacteria have been developed (Table 2). Most of the newer BL/BLIs have targeted ESBL and KPC-producing Enterobacterales (CZA, MVB, and IMI/REL) or multidrug-resistant *P. aeruginosa* (C/T, CZA, and IMI/REL). CZA in particular remains a viable option for infections caused by OXA-48-like producing Enterobacterales. The approval of SUL/DUR added a much-needed agent for the treatment of CRAB, including those producing OXA-23. Remaining gaps in our BL/BLI treatment armamentarium include agents with activity against MBL. For now, the combination of aztreonam with CZA has served to fill this gap. Fortunately, the increased efforts in identifying new BL/BLI combinations with MBL activity are bearing fruit with combinations now close to approval (FEP/TAN, ATM/AVI) or in late development stages (xeruborbactam and nacubactam combinations). Nevertheless, continued development efforts will be required to compete with evolving gram-negative resistance.

AUTHOR CONTRIBUTIONS

Joseph L. Kuti developed the concept and outline. Christina Konig performed the review and wrote the manuscript. All authors reviewed, edited, and approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

J.L.K. reports grants from Merck & Co, Inc, Shionogi, Entasis, the United States Food and Drug Administration, Biomeriuex, Roche, consulting fees and payment or honoraria for lectures from Shionogi. C.K. has received consulting fees and honoraria for lectures from Shionogi, Pfizer and Gilead, and reports grants from the DAMP and Joachim Herz Foundations.

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